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Quinidine in maintenance of sinus rhythm after electroconversion of chronic atrial fibrillation
A controlled clinical study

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One hundred patients were subjected to a controlled study of the effectiveness of quinidine treatment upon the maintenance of sinus rhythm after electroconversion. The quinidine series was treated with a long-acting preparation of quinidine sulphate, which was given in a dosage to achieve serum levels between 4 and 6 mg/l. The control series received no quinidine. The maintenance rate did not differ significantly in the two series during the first three months, but for the remaining observation time until 12 months a significant difference in favour of quinidine was present. Identical results were found in a cross-over experiment, in which 24 patients served as their own controls. Further analysis brought forward that quinidine was effective only if the atrial fibrillation had lasted for less than one year before electroconversion. Complications due to the use of quinidine were negligible during the observation time.

Electroconversion of atrial fibrillation has proved so safe and effective that the main problem at present is to find measures for maintenance of the obtained sinus rhythm.

In this respect the well-known antiarrhythmic properties of quinidine have received wide attention. Maintenance treatment with this agent has, however, yielded controversial results. It has been found effective by some authors (Korsgren *et al.*, 1965; Rossi and Lown, 1967; Lown, 1967), and ineffective by others (Oram and Davies, 1964; Halmos, 1966; Szekely, Batson, and Stark, 1966; Engström, 1967; Hall and Wood, 1968). In addition, the dangerous side effects of quinidine have been currently documented (Oram and Davies, 1964; Bjerkelund and Skåland, 1967; Åberg, 1969; *British Medical Journal*, 1969) and contributed to the reluctant attitude towards the use of quinidine as a maintenance treatment. It seems very necessary therefore to conduct controlled clinical studies.

Recently this need has been met by two such studies (Härtel *et al.*, 1970; Byrne-Quinn and Wing, 1970), both showing the effectiveness of quinidine in preserving sinus rhythm after electroconversion. Moreover, these useful studies indicate the advantage of controlling the serum levels of quinidine in order to avoid adverse reactions to the treatment with this agent.

The present study was started in 1968 and is still under way. The reason for giving the results at this time is the fact that the first 100 patients have now been under observation for 12 months or more. Thus the effectiveness of quinidine as maintenance treatment can be elucidated. Moreover, the present report clearly points to the importance of the duration of atrial fibrillation for the correct evaluation of the effectiveness of quinidine.

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Patients and methods

The patients were randomly allocated into two groups, one receiving quinidine therapy and the other not. Placebo tablets were not used.

Digitalis was regularly discontinued 2 to 4 days before electroconversion and quinidine treatment was simultaneously started. The preparation used was a long-acting tablet containing 0·2 g quinidine sulphate coated with cellulose acetate phtalate (Lindseth Ditlefsen and Bjerkelund, 1966). It was given twice daily in a total daily dosage of about 0·8 g to 1·2 g to keep the serum level of quinidine between 4 and 6 mg/l. The serum level of quinidine has been found to remain constant

over long periods of time with this preparation provided the dosage is kept unchanged. The quinidine concentration of serum was estimated according to the method of Balatre, Lefevre, and Merlen (1960).

Electroconversion was carried out in the ordinary way under light general anaesthesia. If the first DC shock with 100 joules was ineffective, the energy was successively raised to 200, 300, and 400 joules. Electroconversion was registered as successful if sinus rhythm was present when the patient left the operating theatre. On the same day digitalis medication was resumed and quinidine treatment continued in the respective patient group.

The patients were followed with regular clinical controls and daily electrocardiograms during the first week. Later controls were undertaken at 1, 3, 6, and 12 months. For geographical reasons most of these controls had to be done far from our hospital. Further estimations of the serum quinidine level could, therefore, be obtained in only a small number of patients.

By relapse the patients and the physician in charge had been told to report immediately to our department for readmission and a second electroconversion. Several of the patients were submitted to a cross-over experiment and became their own controls with respect to the effectiveness of quinidine as maintenance therapy.

Permanent anticoagulant treatment was given to all the patients in accordance with the results of a recent study from our department (Bjerkelund and Orning, 1969).

Results

The quinidine and the control series were similar with regard to sex, age, and heart size, while the duration of atrial fibrillation was slightly longer in the control series (Table 1).

The distribution within the two series according to aetiology of atrial fibrillation was also comparable (Table 2). In both groups rheumatic mitral valve disease accounted for more than 50 per cent of the diagnoses.

Three patients obtained restoration of sinus rhythm during pretreatment with quinidine. These are not excluded from the quinidine series.

The results of the trial are given in Fig. 1. The restoration rate is identical in both groups as is the persistence of the sinus rhythm during the first week. A difference in favour of quinidine is present for the remaining time of observation, but it is significant only after 6 months.

The results of the cross-over experiment corroborate the above conclusion (Fig. 2), though the number of patients is too small for statistical analysis. The difference in favour of quinidine is conspicuous both at 6 and 12 months of observation.

The mean serum level of quinidine for those who obtained sinus rhythm by electroconversion was 3·1 mg/l. against 2·8 mg/l. for those who did not revert. The difference is not statistically significant. Neither is the difference between the mean energy of 140 joules required to obtain sinus rhythm in the quinidine series against the mean energy of 150 joules required in the control series.

TABLE 1 *Distribution of patients given quinidine or no prophylactic according to sex, age, duration of atrial fibrillation, and heart size*

	Quinidine series			*Control series*		
	Female	*Male*	*Total*	*Female*	*Male*	*Total*
No. of patients	24	24	48	30	22	52
Age (yr)						
Mean	51	56	54	53	56	54
Range			22–77			35–75
Duration of atrial fibrillation (mth)						
0–6	10	12	22	11	5	16
7–24	9	3	12	10	5	15
24	5	10	15	9	12	21
Heart size (ml/m² BSA)						
Mean	600	637	618	604	679	648
Range			270–930			345–930

TABLE 2 *Aetiology of atrial fibrillation in patients given quinidine or no prophylactic*

	Quinidine series	*Control series*
No. of patients	48	52
Rheumatic heart disease		
Mitral valve disease	29	27
Aortic valve disease	6	7
Atherosclerotic heart disease	5	5
Lone fibrillation	4	4
Thyrotoxic cardiomyopathy	2	2
Congenital heart disease	1	2
Chronic myocarditis	1	4
Myxoma cordis	0	1

An attempt was made to elucidate the effect of various heart sizes on the maintenance rate. This was, however, impossible to decide, because the vast majority of cases had heart volumes around 700 ml/m² body surface.

In contrast, the duration of atrial fibrillation prior to electroconversion obviously affected the maintenance rate. Analysis indicated that the most obvious distinctions were present when duration was considered in terms of less than or more than one year (Table 3). It then becomes clear that quinidine is effective as maintenance treatment only when atrial fibrillation has lasted for less than one year. The difference in maintenance rate in comparison with the quinidine treated group with duration of the arrhythmia of more than one year is significant at the time of 6 months ($P < 0.01$) as well as at the time of 12 months ($P < 0.05$). It is also clear that the maintenance rate is identical for the quinidine-treated group with

duration of the arrhythmia over one year and the untreated group with duration of less than one year. Finally, there is within the control series a slightly better maintenance rate in the group with duration of less than one year, but a significant difference is not present at any time. The important conclusion, therefore, is that quinidine treatment is effective only when atrial fibrillation has been present for less than one year before electroconversion.

It is well known that relapse to atrial fibrillation mainly takes place during the first three months after conversion (Byrne-Quinn and Wing, 1970). In the present study the relapse rate is not very different during the first three months as compared with the following nine months (Table 4). Again the positive effect of quinidine on the maintenance rate is seen for atrial fibrillation of less than one year's duration.

The complications encountered in the present study were few. A woman succumbed from a cerebrovascular insult one month after successful electroconversion, probably due to a relapse with subsequent embolization. She was under correctly administered anticoagulant treatment at the time. Two men under treatment with quinidine got severe diarrhoea, which disappeared by substituting quinidine with quinine. Another man also got diarrhoea on quinidine treatment, which he therefore stopped with the result that his arrhythmia relapsed. He was excluded from the trial. A woman had syncope during pretreatment with quinidine: no signs of ventricular asystole or fibrillation could be seen, and the quinidine concentration in serum was only 2·9 mg/l. Quinidine was therefore not held responsible for the syncope and the treatment was continued without complications.

Evidence has recently been presented on the risk of occurrence of early complications by electroconversion when pretreatment with quinidine is given (Åberg, 1969). Corresponding evidence from the present study will be discussed in a forthcoming paper (Hillestad, Dale, and Storstein, 1971).

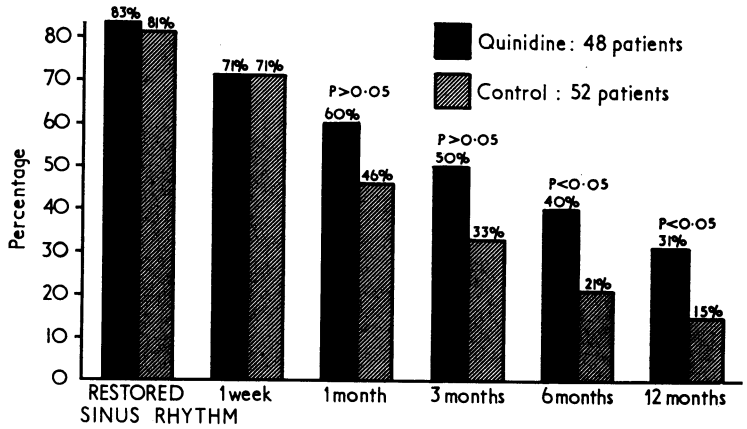

FIG. 1 *Effect of quinidine on the maintenance of sinus rhythm after electroconversion.*

Discussion

This study shows that quinidine is effective in the maintenance of sinus rhythm after electroconversion. It thus corroborates the results of the two other controlled studies (Härtel *et al.*, 1970; Byrne-Quinn and Wing, 1970).

There are, however, some small differences between these reports. In the Finnish study the patients were observed for only three months (Härtel *et al.*, 1970), but at that time a significant difference in favour of quinidine was present. In the English study (Byrne-Quinn and Wing, 1970) a similar difference was present from the third month and up to the end of the observation time at 15 months. The series was, however, small. In the present study the occurrence of a corresponding significant difference was delayed until the observation at 6 months and was still present at the control at 12 months. Thus a real long-term effect of quinidine was seen.

Most impressive was the observed effect of the duration of the arrhythmia upon the maintenance rate. In the Finnish study this problem is not considered, while the duration was equal in the various groups of the English study. The effect of duration upon the maintenance rate is otherwise well documented

FIG. 2 *Effect of quinidine on the maintenance of sinus rhythm in the cross-over experiment on primary failures. A total of 24 patients served as their own controls.*

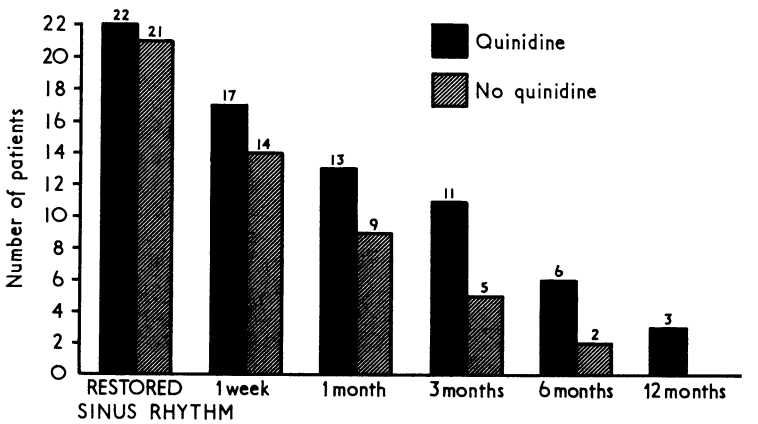

TABLE 3 *Relation between duration of atrial fibrillation and maintenance of sinus rhythm after conversion*

Duration of atrial fibrillation	*Quinidine series*		*Control series*	
	< 1 yr	*> 1 yr*	*< 1 yr*	*> 1 yr*
No. of patients	26	22	22	30
Sinus rhythm restored	20	20	20	22
Sinus rhythm after:				
1 week	17	17	18	19
1 month	15	14	12	12
3 months	15	9	9	7
6 months	14	5	6	5
12 months	12	4	6	2

TABLE 4 *Relapse rate of quinidine and control series according to observation time*

Duration of atrial fibrillation	*Quinidine series*			*Control series*		
	< yr	*> 1 yr*	*Total*	*< 1 yr*	*> 1 yr*	*Total*
Relapse (%)						
0–3 mth	25	55	40	55	70	62
4–12 mth	20	56	33	33	71	50

(Bjerkelund and Orning, 1968) and must consequently be accounted for also in corresponding studies on quinidine. The reason that previous studies have failed in finding this agent effective as maintenance therapy may partly be due to neglect of the role played by the duration of the atrial fibrillation. In addition, small series, lack of control of the serum levels of quinidine, and the use of ordinary quinidine sulphate may have contributed.

There seems to be agreement that long-acting quinidine preparations have distinct advantages (Härtel *et al.*, 1970; Byrne-Quinn and Wing, 1970). These give stable serum levels so that ineffectively low as well as dangerously high levels are avoided. A similar agreement exists with regard to the necessity of controlling the serum concentration of quinidine. While the latter is constant in the individual patient on a given dosage, equal dosage can produce different values in different patients (Cramér, 1968).

It is a fact that a considerable number of patients remain in sinus rhythm for a long time after electroconversion without antiarrhythmic treatment. The Finnish report (Härtel *et al.*, 1970) therefore recommends that electroconversion should be carried out first without such treatment, but that maintenance therapy with quinidine be instituted at the second conversion. This approach is based on sound clinical judgement of the advantages and dangers of quinidine treatment. The present report adds one important conclusion, namely that quinidine, whenever given to preserve sinus rhythm, should only be given to patients who have had atrial fibrillation for less than one year before electroconversion.

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